DECEMBER 10, 1984
CHEMICAL & ENGINEERING

NEWS

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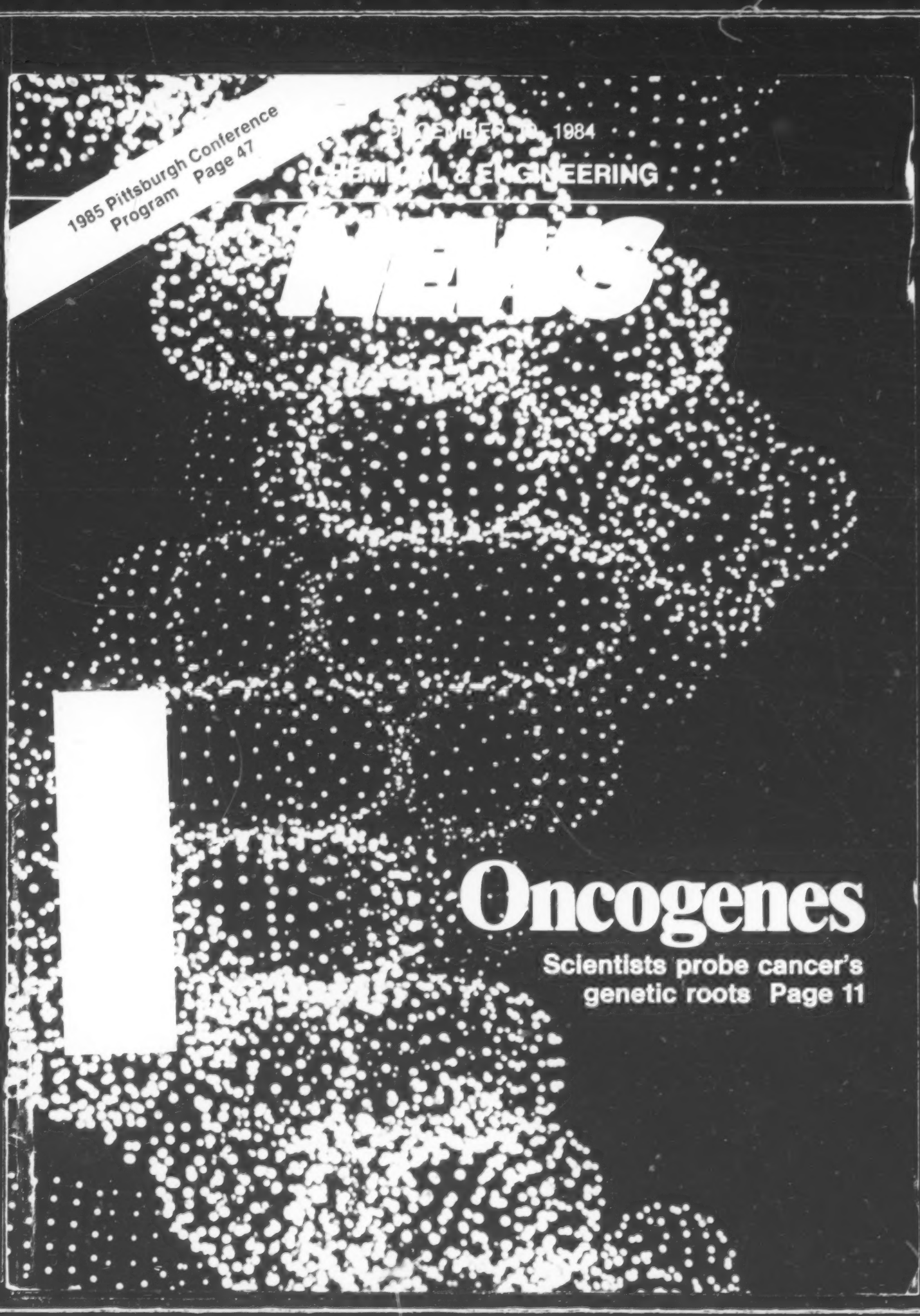

Oncogenes

Scientists probe cancer's genetic roots Page 11

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NEWS

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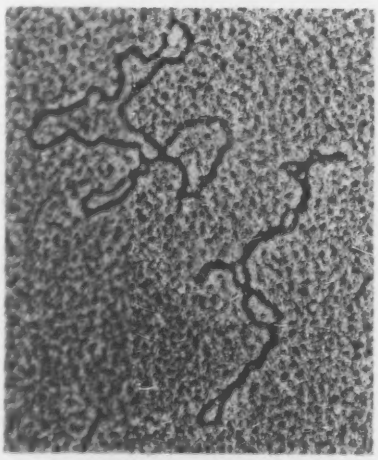
Cover: Computer graphics-generated view of B form of DNA produced by Computer Graphics Laboratory, University of California, San Francisco. Red dots describe oxygen atoms, blue nitrogen, green carbon, yellow phosphorus, and white hydrogen. Copyright University of California



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Oncogenes—genes in human cells that can transform the cells from normal to cancerous—are one focus of cancer research today. Page 11

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Biotechnology Firms Gird For Clash over Patent Claims

As more biotechnology patents are issued, disputes multiply, leading more companies to beef up their patent departments

David Webber, C&EN New York

One necessary task this past year for the fledgling companies that make up the small-firm portion of the biotechnology-related industry has been to mesh their scientific prowess with equivalent business capability. In the ongoing transition from an array of research and development boutiques to commercial entities with products, the small entrepreneurial companies have vigorously recruited marketing and production experience from the pharmaceutical and chemical industries. Top managers from Dow Chemical, Du Pont, and several drug houses have made the jump to the small side.

Most of the new employees have been brought on to help answer the broad questions of which products to commercialize, which to license, and which, in some cases, to abandon. At the same time, however, the firms have not lost sight of the proposition that, as with any new technology, biotechnology opportunities will depend to a great extent on protection of intellectual property. In a year that saw the foundations laid for the first major biotechnology patent dispute—between Biogen and Hoffmann-La Roche over Biogen's European patent on α-interferon—companies have moved to beef up their patent departments as well.

Earlier this year, for example, Genentech, the most prominent

Kline: litigation will play key role

smaller company in the field, hired a 32-year veteran of Eli Lilly and a nine-year veteran of Travenol Laboratories as chief patent counsel and senior patent counsel, respectively. "The addition of these key experts is a strong indication of the importance Genentech places on patents," says president and chief executive officer Robert A. Swanson. "As we approach the marketplace, we expect our products to be well protected by patents. We also will have the capability to enforce those patents, where required to prevent others from capitalizing on our investment in pioneering research."

This kind of tough talk is becoming more common as companies begin to clash over patent claims. Because in many cases several companies are using the various techniques of biotechnology to seek the same or similar products, it is widely expected that the industry will be a very litigious one in the years to come.

"Litigation is going to play a very important role in this area over the next few years," says Robert C. Kline, chief counsel of Du Pont's patent division. That's "primarily because there are some areas of uncertainty, but in addition to that, you've got an awful lot of [people] out there who are investing an awful lot of money in this thing for the future. And the upshot of that is that when you've got a number of people who are going to be plowing in the same field, so to speak, it is going to lead to litigation."

What those in the biotechnology field are trying to gauge now is to what extent litigation is inevitable in their particular area and to what extent it is avoidable—and at what price. Patent litigation is considered one of the costliest types of legal dispute. For the smaller companies in the field, especially, there are undoubtedly some difficult choices ahead in terms of which inventions they can afford to defend.

Consequently, those companies and their large counterparts as well would like to see certain aspects of the patent situation clarified. Although biotechnology's gray areas in the patent arena are similar in the main to those of other advanced technologies, there are questions relating to such aspects as the breadth of patent claims, the ability to differentiate one invention from another, and the patentability itself of some potential products that many experts consider unique to the field.

Disputes seem certain to increase as more and more patent applications are filed. The volume of biotechnology-related patent applications has increased sharply each year for the past several years. According to the U.S. International Trade Commission's study on inter-

WORLD CHEMICAL OUTLOOK

SPECIAL REPORT

This year is slated to go into the books as a period of solid growth for the chemical industry throughout the world.

Increased demand from a host of chemical-consuming industries has led producers in the U.S. and other parts of North America, in Western Europe, in Japan, and elsewhere to boost their output and has sparked a healthy improvement in earnings.

The rebound, however, has not dispelled several long-standing problems. Competition in world markets remains stiff—and is expected to become more intense during the next year or two as new producers of petrochemicals strive to carve out a share of world trade. The unprecedented strength of the U.S. dollar, meanwhile, has severely disadvantaged U.S. chemical companies, both at home and abroad.

Now, moreover, concern is rising that growth in chemical consumption is slackening. If it indeed is, the persistent threat of excess capacity and inadequate return on investment may continue to bedevil the industry. Chemical companies recently have taken giant steps to improve efficiency, rein in operating costs, and seek out new, more lucrative markets. A period of slower, if any, growth is likely to retest their mettle and to demonstrate just how meaningful the changes of the past few years actually are.

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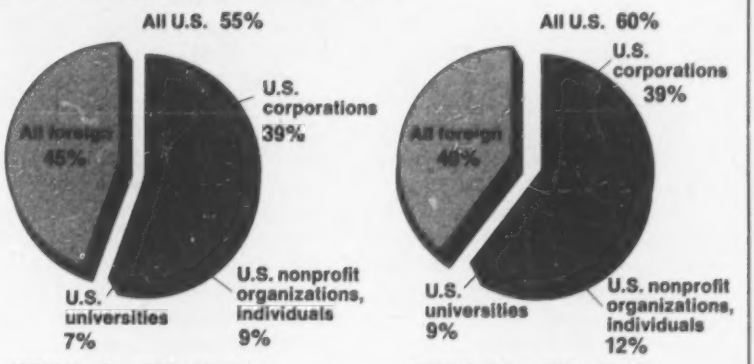
national developments in biotechnology, released in October, the number of such patents issued by the U.S. Patent & Trademark Office grew from 92 in 1979 to 234 in 1980, 313 in 1981, and 372 in 1982. (These figures, based on official Commerce Department statistics, are cited from a patent office study of six areas of biotechnological products and processes.)

The proliferation of biotechnology-related patents is hardly surprising, considering the speed with which advances are being made. Less expected, perhaps, is the pattern of patent activity. Of 826 biotechnology-related patents assigned by the Patent & Trademark Office during the first nine months of 1984, a total of 326, or some 40% of them, were assigned to foreign parties, according to a survey of data compiled by OMEC International, a Washington, D.C.-based consulting firm. Of the 500 granted to U.S. parties, OMEC's survey points out, 321 were assigned to domestic corporations, 78 to universities (or related bodies), and 101 to individuals and nonprofit organizations such as Research Corp.

The pattern is not a one-time phenomenon. Surveying data for the first nine months of 1983 (for comparative purposes), OMEC finds that, of a grand total of 734 biotechnology-related patents, 45% were assigned to foreign parties, and the 55% gained by U.S. concerns were distributed about as they were this year among corporations, academia, nonprofit bodies, and individuals. Similarly, the patent office study cited in the ITC report put the foreign to domestic ratio of such patents at 51:49 in 1979, 49:51 in 1980, 45:55 in 1981, and 43:57 in 1982.

Although the share of each year's biotechnology-related patents assigned to foreign parties has been shrinking steadily, it is still large —a sign of overseas inventors' assiduousness in staking out places for themselves in the U.S. market. In terms of individual countries of origin for U.S. patents in the field, the most active by far has been Japan. According to OMEC, for instance, Japanese inventors accounted for 46% of such patents assigned to

Foreign concerns gain large share of U.S. biotechnology-related patents



* First nine months. Source: OMEC International

foreign parties in the first nine months of 1984, up from 42% in the equivalent 1983 period. The other major foreign countries of origin have been West Germany, Britain, and France.

Oskar R. Zaborsky, president of OMEC and a former program director at the National Science Foundation, notes two other aspects of biotechnology-related patent activity so far. First, he points out, despite the greater amount of attention paid to the smaller biotechnology-based firms, most of the patents in the field assigned to date are owned by large corporations. Over the first nine months of 1984, for example, companies such as Du Pont, Hoffmann-La Roche, Eli Lilly, Merck, Miles Laboratories, and Upjohn were assigned 10 or more biotechnology patents. By comparison, well-known small companies gained far fewer patents. For example, Genentech won five patents, Cetus three, Genex one, Molecular Genetics one, and Biogen, Collaborative

Large corporations get most biotechnology-related patents

	Patents assigned[a] 1984[b]	1983[b]		Patents assigned[a] 1984[b]	1983[b]
Agrigenetics	5	1	Lever Brothers	4	2
Agromate	3	13	Eli Lilly	11	10
Baxter-Travenol Laboratories	8	3	Merck	21	25
Battelle Research Laboratories	0	0	Miles Laboratories	17	14
Biogen	0	0	Molecular Genetics	1	0
Boehringer Mannheim	2	8	Monoclonal Antibodies	0	0
Cetus	3	0	Nabisco	8	5
Collaborative Research	0	0	Novo Industri	2	3
Corning Glass Works	1	2	Ortho Diagnostics	5	1
Damon Biotech	0	1	Pfizer	7	5
Du Pont	10	2	Phillips Petroleum	5	4
Elco Biochem	0	0	Sanraku-Ocean	4	1
Genentech	5	0	Smithkline Beckman	2	2
Genex	1	1	Stauffer Chemical	3	2
Green Cross	2	2	Takeda Chemical Industries	7	4
Hoffmann-La Roche	10	14	Upjohn	10	6
Hybritech	0	1	Other	423	425
Kyowa Hakko Kogyo	4	4	TOTAL	582	581

[a] Biotechnology-related patents assigned by U.S. Patent & Trademark Office to U.S. and foreign-owned corporations. Selection of individual companies intended as a cross section of industrial activity. [b] Data are for first nine months of each year. Source: OMEC International

Foreign patents may offer less protection

Despite industry's complaints about the performance of the U.S. Patent & Trademark Office and anxiety over patent uncertainties, there is a widespread belief that U.S. patent law probably will work out to protect biotechnology-related inventions better than foreign patent systems.

"It's perhaps fair to say that the patent laws in the U.S. provide for a better degree of protection in biotechnology than the laws in many other countries," says Robert C. Kline, chief counsel in Du Pont's patent division.

U.S. patent law includes a number of incentives for inventors to file for a patent application that do not exist in Japan and Western Europe. For instance, in the U.S., inventors have a one-year grace period between the time a written description of their invention is made publicly available and the date of the filing of a patent application. By comparison, the Japanese grace period is just six months, and in Western Europe there is no grace period at all.

Also, the U.S. patent office keeps a patent application secret and the inventor's culture microorganism unavailable to the public until the patent issues. In Europe, on the other hand, anyone can inspect the application (usually for 18 months) after filing, regardless of whether a patent is ultimately granted.

Another advantage of the U.S. system to inventors is that if there are several different inventors applying for a patent on the same invention at the same time, the patent is awarded to the applicant who was the first to make the invention. In Western Europe and Japan, by contrast, it is the first party to file an application that gets priority.

Perhaps most important to those who would protect their biotechnology inventions in the U.S. is the patent office's apparently broad interpretation of what is patentable. U.S. patent policy seems to allow the inclusion of plants and animal types and the biological methods for producing them. The European Patent Convention, on the other hand, deems new plants and animal types unpatentable. Japan excludes from patent consideration inventions that involve unclear processes or methods.

"The U.S. appears to offer a competitive advantage over Europe and Japan in encouraging inventors to file for patents rather than to keep the invention a trade secret," comments the International Trade Commission's October assessment of international developments in biotechnology.

But U.S. biotechnology firms are less happy about the U.S. failure to define as patent infringement the use of a process—already patented in the U.S.—outside the U.S. by a competitor to the patentee, since the product made by this process can then be imported back into the U.S. A provision that would have amended that policy was deleted from a bill (H.R. 6286) passed by the recent Congress that included other changes in patent law.

Research, Damon Biotech, Enzo Biochem, Hybritech, and Monoclonal Antibodies, none.

Second, Zaborsky comments, universities are gaining nearly a fourth as many biotechnology patents as are U.S. corporations, a level he calls "amazingly" high. "This is a trend," he says. "More universities are patenting their faculty inventions."

The rapid proliferation of biotechnology patent applications has put the patent office to the test, and, so far, the examiners have drawn mixed reviews from members of industry. The patent office has been criticized for slowness in processing applications and for inadequate scientific expertise on its staff of examiners.

"A lot of questions remain as to what can be defined as unique, and the [patent office] staff probably could use more people to make that judgment," remarks Zsolt Harsanyi, a biotechnology consultant to Porton International, a British biotechnology firm, and to E. F. Hutton. "People filing applications have said to me that they're having real trouble explaining what the concept is to the people at the [patent office]. They get remarks back that to them indicate that perhaps the point was missed."

Harsanyi, in an assessment that

Japanese lead other foreign firms in biotechnology patent activity in U.S.

	Patents assigned[a]			
	1984[b]	% foreign total	1983[b]	% foreign total
Japan	149	45.7%	139	41.6%
West Germany	57	17.5	47	14.1
Great Britain	30	9.2	15	4.5
France	19	5.8	31	9.3
Canada	8	2.4	13	3.9
Netherlands	7	2.2	14	4.2
Italy	7	2.2	13	3.9
Switzerland	7	2.2	11	3.3
Denmark	7	2.2	9	2.7
Sweden	7	2.2	8	2.4
Belgium	5	1.5	0	0.0
U.S.S.R., Eastern Bloc	4	1.2	15	4.5
Australia	3	0.9	1	0.3
Austria	1	0.3	3	1.2
Israel	1	0.3	4	0.9
Other	14	4.3	11	3.3
TOTAL	326	100.0%	334	100.0%

a Biotechnology-related patents assigned by U.S. Patent & Trademark Office to foreign-owned companies. b Totals are for first nine months of each year.
Source: OMEC International

Harsanyi: question of uniqueness

Academic biotechnology patent activity dominated by a handful of universities

	Patents assigned[a]			
	1984[b]	% university total	1983[b]	% university total
University of California[c]	15	19.2%	10	20.4%
Cornell University	5	6.4	2	4.1
Stanford University	5	6.4	2	4.1
University of Wisconsin	5	6.4	3	6.1
Harvard University	4	5.1	4	8.2
Purdue University	3	3.8	1	2.0
University of Illinois	2	2.6	0	0.0
Iowa State University	2	2.6	1	2.0
Massachusetts Institute of Technology	2	2.6	5	10.2
Montana State University	2	2.6	1	2.0
Northwestern University	2	2.6	1	2.0
Other	31	39.7	19	38.9
TOTAL	78	100.0%	49	100.0%

a Biotechnology-related patents assigned by U.S. Patent & Trademark Office to U.S. universities. b Data are for the first nine months of each year. c Entire university system. Majority are University of California, Berkeley. **Source:** OMEC International

others in the field have made as well, says that the patent office has approved patents for inventions and processes that seem obvious to those practicing the science. "I've looked at a couple of vaccine applications, and for the life of me, I can't believe how the claims were ever allowed. To me, some of the claims that were made were quite well known in the field," he says.

Well aware of such criticism, the patent office has taken a number of remedial steps, both in response to the particular complaints of the biotechnology field and as part of a broad, long-term effort to beef up performance in all areas. In the general area, the patent office is moving on three major goals—to bring the period between a patent's filing date and disposal of the application down to 18 months; to bring the pendency period for trademark applications down to 13 months; and to automate search operations by 1990.

Still, the patent office currently is working on a backlog of some 1000 applications in the genetic engineering area and 2600 in the broader biotechnology field (including genetic engineering). The average pendency for both categories has now stretched out to some 28 months, according to Rene D. Tegtmeyer, assistant commissioner for patents in the patent office. Part of the problem, Tegtmeyer explains, is lack of staff. There are now just 26 patent examiners in the biotechnology area, with only 12 of them concentrating on recombinant DNA-based inventions. Although the patent office is planning to increase the genetic engineering examiner staff to 20 and the biotechnology total to 40 by next September, Tegtmeyer warns that it takes four to five years before exa niners are fully proficien' in their area.

To counter this problem, the patent office has made several organizational and procedural changes in an effort to streamline the process and improve the quality of patent examination. Previously, for instance, applications related to biotechnology were distributed among a half-dozen examining groups in the patent office. Now, almost all such patents are consolidated within two subgroups—or "art units" —of one examining group. Other changes include greater attention to training examiners and a "special status" mechanism to speed up disposal of applications that meet certain requirements. According to the patent office's Tegtmeyer, so far there has been only one request for priority attention in the genetic engineering area.

Price: a period of uncertainty

Those and other measures are generally pleasing to industry. "I think the government [patent agency] is probably not moving as fast as we'd like, but at least it's moving in a pretty good direction for us on this," says John E. Donalds, president of Collaborative Research, Lexington, Mass.

But although the patent office adjustments seem a good response to the mechanical problems of biotechnology patenting, biotechnology inventors are not expecting the philosophical questions in the area to be answered quite so succinctly. The patent office has indicated that it expects the courts to settle many of the thornier debates. What those in industry, academia, and elsewhere can definitely anticipate is that much of the biotechnology patent gray area will be illuminated on a case-by-case basis.

"The issue is not really whether patent law will be adequate, but the issue is that there will be some period of uncertainty while details are being sorted out," comments Harvey S. Price, executive director of the Industrial Biotechnology Association. "Of course, it will be in the industry's interest if these things are sorted out in a shorter time frame rather than in a longer time frame." □